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TEMPERATURE CHANGES IN
THE CORTEX AND HYPOTHALAMUS
DURING SLEEP

A DISSERTATION SUBMITTED TO THE
FACULTY OF THE DIVISION OF THE
BIOLOGICAL SCIENCES IN CANDIDACY FOR
THE DEGREE OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF PHYSIOLOGY

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HERMAN M. SEROTA

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TEMPERATURE CHANGES IN THE CORTEX AND HYPOTHALAMUS DURING SLEEP*

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THE EXISTENCE of a "sleep center" is now established by animal experiments and clinical data supplemented by necropsy material. The localization of such a center has been much studied and the literature, adequately reviewed by Rowe, places it in the diencephalon, in the hypothalamus, or in the floor of the third ventricle. The mechanism of its function, however, has received little attention. Hess (1931, 1932) has stimulated the sleep area electrically through fine platinum electrodes embedded in the brains of otherwise normal animals and elicited true sleep, easily repeatable in the same animal. On the basis of this and other observations, such as pupillary constriction and increased intestinal mobility during normal sleep, he postulates the existence of a parasympathetic center which, by increasing its activity, leads to sleep. This implies the discharge from it of sleep-producing impulses.

In the human (Fulton and Bailey, 1929) and the cat (Ranson, 1934), however, sleep and somnolence are the usual outcome of destructive lesions in the same area. Further, Ranson has elicited rage reactions rather than sleep by hypothalamic stimulation. The seeming conflict in producing sleep by stimulation or destruction of a localized "sleep center" demands further study. It is conceivable that an actively functioning sleep center should manifest an increase in metabolism while other regions, *e.g.*, the cortex, show a decrease during sleep. The technique devised for the localization of thermal changes in the cat brain (Serota and Gerard) was therefore adapted to the study of this problem.

METHOD

Twenty-six cats were operated on aseptically under intraperitoneal nembutal anaesthesia, and two or three thermal needles inserted into the brain with the aid of the Horsley-Clarke instrument. Through small skin incisions and narrow drill holes the needles were lowered to the proper depth and then secured by sterile wooden wedges, dental cement, or Duco cement, spread uniformly within a hollow brass screw. The animal was allowed 18 to 24 hours recovery before study. Post-operative pain or infection was minimal, and most animals were active and ate within a day or a day and a half. Only docile cats with like weight and skull characteristics were used.

Thermocouples were made of 38 gauge enameled copper and constantin wire and were further insulated at the bared junction with Duco cement or Bakelite varnish. The extracalvarial portion was covered with waxed linen, rubber, or gutta percha to guard against fortuitous fluctuations in environmental temperature. These insulated wires were connected to binding posts on a cap or collar fixed on the animal. From these, low resistance cables of the same wire connected the constantin, through a constant temperature junction, and the copper, directly, to the galvanometer circuit. The resistance of the thermocouples was 25 ohms, that of the galvanometer, 30 ohms. The sensitivity used in these experiments was $10 \text{ mm.} = 0.1^\circ\text{C.}$, the galvanometer being slightly overdamped. While the

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animal behaved in a normal manner, pacing about the cage, eating or sleeping, temperature readings of each area were made every 3 minutes, the shift from one thermoneedle to another requiring only 15 sec. The hypothalamic lead was placed within the following boundaries (Ranson): 6 to 12 mm. anterior, 0 to -5 mm. vertical and 1 to 4 mm. lateral. The cortical leads were variously inserted in the suprasylvian, lateral, and splenial gyri, from 16 mm. anterior to 2 mm. posterior to the interaural plane, and from 2 to 5 mm. below the dura. The position was checked by gross section.

The criteria of sleep were: the assumption of the "sleep position" (LDCU, *i.e.*, lying down curled up, Fig. 1), and its maintenance for at least 20 minutes; respirations fewer than 20 per min.; few full-bodied movements or changes of position; and refractoriness to noise (*e.g.*, no response to dropping a metal weight on the table). By all these tests an animal nearly always slept shortly after a satisfying meal. Other occasional "naps" or resting periods were easily excluded.



FIG. 1. A typical variant of the "sleep position" in which the animal lies down curled up, "LDCU." (Photographed by Dr. L. L. Robbins.)

RESULTS

The hypothalamus is consistently 0.1 to 0.5°C. warmer than the cortex. This difference fluctuates considerably during the waking state but remains positive at all times. While the animal paces about the cage, sits, cleans itself, or eats, the temperature curves of these areas rise and fall as much as 0.2°C. The variations plot an irregular saw-toothed curve, each tooth lasting from 6 to 12 min. and at times recurring in a definite rhythm or coincident with gross skeletal movements, (Fig. 2). Other more regular temperature changes accompany definite behavior. Thus, during the obvious excitement which follows the sight and smell of food, the temperatures of both hypothalamus and cortex rise, but the former increases more. When food is eaten, both temperatures drop, and the change in the hypothalamus is again greater. (The temperature drop is a direct cooling effect of the food on the blood, for eating warm food leads to a rise.) Defecation and urination also result in a temperature fall. When the animal lies or crouches, both temperatures fall.

In all of these instances both structures appear to change temperature simultaneously.

During the somnolence which frequently follows a meal, while the animal nods and crouches, the temperature curves become irregularly rhythmical, both the temperatures and their difference (hypothalamus minus cortex) rising and falling by 0.1°C . over intervals of 6 min. Prior to the assumption of the "sleep position" there is usually a rise in the hypothalamic temperature, and when the animal curls up on its side and sleeps both the temperatures and the difference between them fall and the jags on the curve are replaced by a reflectively flat plateau (Fig. 2). The hypothalamic temperature may drop

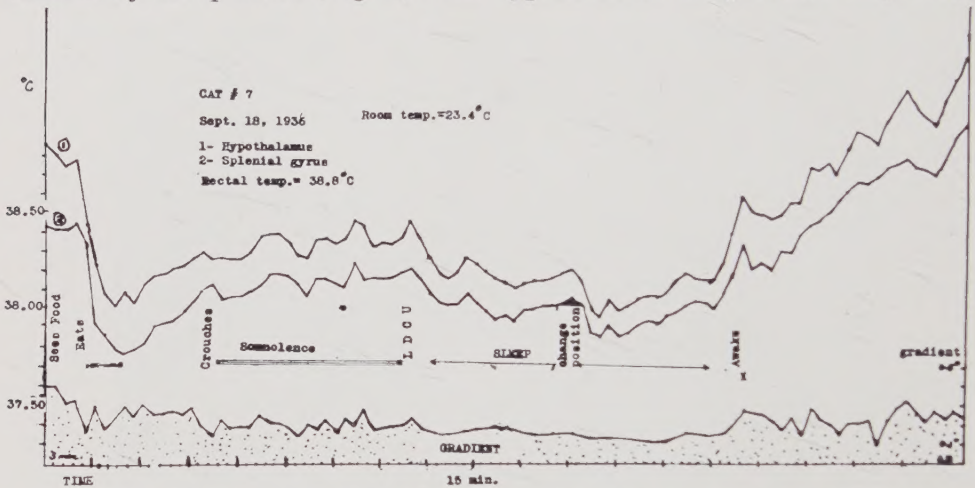


FIG. 2. Characteristic findings in sleep. Ordinate, temperature in degrees Centigrade; abscissa, time in 15 min. intervals. Two thermocouples, a cortical and hypothalamic, are simultaneously followed at 3 min. intervals. LDCU represents assumption of the "sleep position." Curve 1, absolute temperature of the hypothalamus; 2, same of the cortex. The stippled area is the temperature difference between them.

as much as 0.4°C . and the cortical only 0.2 , so that the difference is reduced by 0.2°C . On waking the changes are reversed, and frequently a temperature increase, seen first in the hypothalamus, precedes the other signs of arousing.

The greater fall, during sleep, of the hypothalamic temperature than that of the cortex is not shared as markedly and consistently by other structures. Thus, a third needle in Ammon's horn or in the tail of the caudate nucleus showed a smaller temperature change than the hypothalamic needle. (These structures are at a depth equivalent to that of the hypothalamus and serve to control any effect of sleep on the pre-existing gradient (Serota and Gerard, 1938). Not all curves fitted the above description. Thus, of 119 curves on 26 animals, 88 showed a fall during sleep, 18, a rise, and 13, no change. About the same proportions hold for each lead. In 80 cases the curve flattened to the typical plateau, sometimes with a rise of temperature. On comparing hypothalamus and cortex the temperature in the former decreased relative to the latter in 31 cases out of 37 and rose in only 1. The temperature of the cornu

and caudate, in contrast, fell relative to that of the cortex in only 7 and rose in 3 cases out of 14.

To determine to what extent the specific cooling of the hypothalamus in sleep was due to diminished metabolic activity of its cells or to change in blood supply, the heated thermo-junction of Gibbs (1933) was used. This responds to greater blood flow by a drop in temperature larger than any changes in the unheated needle (Serota and Gerard, 1938). The heated needle

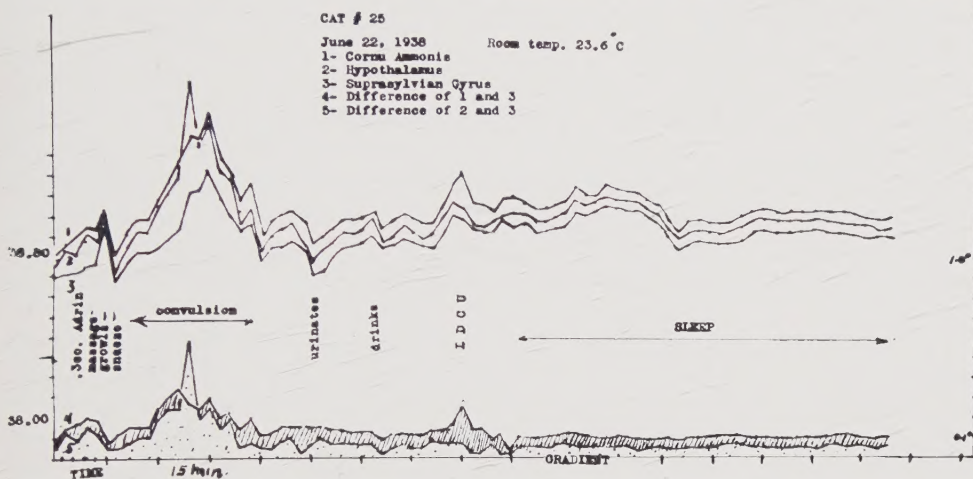


FIG. 3. Minor convulsion induced by epinephrin injection. Ordinate and abscissa as in Fig. 2. The temperature changes recorded by three thermocouples placed in the Cornu Ammonis, the hypothalamus, and cortex, are followed in curves 1, 2 and 3 respectively. Curve 4 represents the temperature difference of curves 1 and 3; and curve 5, of 2 and 3. Following the subcutaneous injection of epinephrin a period of hyperkinesis, ataxia and hypertonia results. This is succeeded by normal behavior and then by deep sleep.

showed only a slight temperature fall during sleep, indicating an insignificant change in blood flow. The validity of this conclusion was further checked by finding that eating either warm or cold food, which increases blood flow, cooled the heated needle, though the unheated needle was warmed or cooled, respectively, by warm or cold food, and by a smaller amount.

It follows that the hypothalamic neurones decrease their activity in sleep. It might be anticipated that in excitement the reverse would occur. Confronting a cat with a barking dog elicited in it the usual emotional storm and increased all brain temperatures, that of the hypothalamus most. A similar stimulation by epinephrin (0.3 cc. of 1-1000 Adrin subcutaneously, followed by local massage) caused hypertonia, ataxia and hyperkinesis amounting to a mild convulsion, and lack of response to a threatening gesture before the eyes. Subcortical temperatures rose more and sooner than that of the cortex and paralleled the motor symptoms, the hypothalamic temperature outstripping the others at the moment of most violent hyperkinesis. As the temperature difference between cortex and hypothalamus subsided, the convulsion ceased, the animal defecated, urinated, ate in the usual manner, lay down, and fell

into an unusually deep sleep (Fig. 3). (Compare the silent period of the EEG after an epileptic discharge.)

Hypothalamic temperature and not others, would frequently rise over a period of 3 to 12 min. during sleep and at its maximum the animal would suddenly shift position. Temperature then fell at once with the attainment of the new position. This continual accumulation of "tension" during sleep, released in muscular movement, has frequently been pointed out (Kleitman, 1929). The hypothalamus apparently plays a role in the discharge of these tensions.

DISCUSSION

The constant alteration in brain temperature during sleep is a smoothing off of the jagged activity curve and a fall in hypothalamic temperature greater than elsewhere. Exceptions occur: the plateau may be broken due to restless sleep with much movement; and a preceding cold meal may have lowered brain temperature before sleep so much (1.0°) that it continues to rise even when sleep sets in. Still other irregularities occur uncommonly and are not explained.

The fall in temperature is not attributable to changed blood flow, as shown above. Gibbs (1935) also failed to find an altered flow in the human jugular during sleep. An increased heat loss from the brain through its coverings (Serota and Gerard, 1938) would affect cortex far more than deeper structures, which is not the case. The only satisfactory explanation of the cooling is a decreased heat production due to diminished neurone metabolism. The findings of Lampl and Feitelberg (1935) further indicate this. A thermocouple in the cat's cortex registered 0.5°C. warmer than that in the carotid artery during ordinary waking activity, 0.2° warmer during rest, and actually lower under paraldehyde anaesthesia.

The greater fall in hypothalamic than in other brain temperatures during sleep indicates a specific diminution of activity of these centers. This is in accord with the findings of Ranson (1934) and of Bard (1928), who found that stimulation of the hypothalamus leads to increased general activity, and indicates that sleep is associated with depression of the hypothalamus rather than its stimulation. The apparently opposed findings of Hess (1931) may perhaps be due to a depression rather than a stimulation of the "sleep center" by the sleep-producing slow currents used by him. Certainly the induction of sleep in his preparations by the injection of ergotoxin into the third ventricle is more easily explained by the view advanced above.

The technique of chronic temperature measurements of local brain regions obviously lends itself to many uses. For example, benzyl-methyl carbinamide (Benzedrine, 10 mg. subcutaneously) has been found (Serota and Schreider, unpublished) to increase temperature in all brain areas studied. The irregularities are supplanted by a smooth parabolic curve which rises and falls symmetrically over a period of four to eight hours, during which time the animal shows minimal increase in motor activity but marked decrease in threshold to faint light or sound stimuli. Serota and Gerard, in preliminary experiments,

have found no evidence of a differential depression of either cortex or thalamus during the anaesthetic action of ether, nembutal, etc.; though all narcotics markedly lower brain temperature in relation to general body temperature.

CONCLUSIONS

A technique is presented for following the temperatures of local brain regions in the unanaesthetized cat.

In the conscious, as in the anaesthetized animal, basal brain regions are warmer than the cortex. Absolute temperatures fluctuate during the waking state, sometimes in a semirhythmic manner, and the positive temperature difference between hypothalamus and cortex increases in irregular fashion with activity.

Emotional states, as fear, rage, or anticipation of food, increase the relative temperature of the hypothalamus; sleep, especially, decreases and stabilizes it.

On awakening from sleep, hypothalamic temperature rises earlier and further than that of the cortex, caudate nucleus, or Ammon's horn.

The specific temperature decrease of the hypothalamus in sleep is shown to be due to lowered cell metabolism rather than to any marked change in blood flow. This indicates that sleep is associated with a decreased rather than an increased activity of a hypothalamic "sleep center."

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